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HEPATIC FIBROSIS AS AN ADDITIONAL RISK FACTOR FOR THE DEVELOPMENT OF CARDIOVASCULAR DISORDERS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS WITH NON-ALCOHOLIC FATTY LIVER DISEASE

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Ключевые слова: *сахарный диабет 2 типа, неалкогольная жировая болезнь печени, сердечно-сосудистые заболевания*

Abstract. *Hepatic fibrosis as an additional risk factor for the development of cardiovascular disorders in patients with type 2 diabetes mellitus with non-alcoholic fatty liver disease. Bilovol O.M., Kniazkova I.I., Zemlianitsyna O.V., Dunaeva I.P., Romanova I.P., Kurilo O.D., Sinaiko V.M., Kravchun N.O. The aim of the study was to determine the relationship between the degree of progression of liver fibrosis and the risk of cardiovascular complications in patients with Type 2 diabetes mellitus (DM) with non-alcoholic fatty liver disease (NAFLD). The study included 110 patients with Type 2 diabetes (62 men and 48 women), the average age of the subjects was 52.07±1.11 years. All patients were divided into 2 groups: the main group included 72 patients with Type 2 diabetes with concomitant NAFLD (38 men and 34 women); the control group included 38 patients with Type 2 diabetes without clinical manifestations of NAFLD (24 men and 14 women). Patients of the main group were divided into 3 subgroups, taking into account the predominant pathological processes in the clinical picture. The division into subgroups was carried out in 2 stages: at the first stage, those with predominant manifestations of liver fibrosis (F2 or more) were selected from the general population of patients with Type 2 diabetes with NAFLD according to the results of liver elastography and the use of Bonacini and Metavir scales. The number of such patients was 29, which accounted for 40.3% of the total number of patients in the main group. The remaining patients were divided into 2 subgroups: 11 patients (15.3%) had non-alcoholic liver steatosis, and 32 patients (44.4%) had signs of non-alcoholic steatohepatitis (NASH). As a result of the study, it was found that the presence of liver fibrosis in patients with Type 2 diabetes with NAFLD is significantly more often associated with cardiovascular complications, such as arterial hypertension,*

coronary heart disease, myocardial infarction, stroke, diabetic retinopathy and nephropathy. A significant decrease in the ejection fraction (EF) was found in patients with Type 2 diabetes with concomitant NAFLD. At the same time, the number of patients with EF disorders of varying degrees in the main group significantly exceeded that in the comparison group (33.3% and 6.7%, respectively, $p < 0.001$). The average values of left ventricular myocardial mass are significantly lower in patients with NASH and fibrosis formation compared to patients with NAFLD at the stage of fatty hepatosis. There was also a significant decrease in the size of the left and right atria in patients with NASH compared to both patients with steatosis and patients with fibrotic liver changes. Patients with predominant fibrotic changes in the liver are characterized by a relative decrease in myocardial mass, a decrease in final diastolic and systolic volumes and EF, which may indicate the development of diastolic dysfunction in them. It is shown that it is necessary to take into account in clinical practice not only the generally accepted stages of NAFLD, but also the predominant pathological process in the liver in patients with Type 2 diabetes, namely steatosis, manifestations of inflammation and fibrotic disorders. It is proved that fibrotic changes in the liver can develop at all stages of liver tissue damage.

Реферат. Фіброз печінки як додатковий чинник ризику розвитку серцево-судинних порушень у хворих на цукровий діабет 2 типу з неалкогольною жировою хворобою печінки. Біловол О. М., Князькова І. І., Земляніцина О. В., Дунаєва І. П., Романова І. П., Курило О. Д., Сінайко В. М., Кравчун Н. О. Метою дослідження було визначення взаємозв'язків між ступенем прогресування фіброзу печінки та ризиком виникнення серцево-судинних ускладнень у хворих на цукровий діабет (ЦД) 2 типу з неалкогольною жировою хворобою печінки (НАЖХП). У дослідження було включено 110 хворих на ЦД 2 типу (62 чоловіки та 48 жінок), середній вік обстежених становив $52,07 \pm 1,11$ року. Усіх пацієнтів було розподілено на 2 групи: до основної групи було включено 72 хворих на ЦД 2 типу із супутньою НАЖХП (38 чоловіків і 34 жінки); контрольну групу склали 38 хворих із ЦД 2 типу без клінічних проявів НАЖБП (24 чоловіки й 14 жінок). Пацієнтів основної групи було розподілено на 3 підгрупи, зважаючи на переважаючі в клінічній картині патологічні процеси. Розподіл на підгрупи було здійснено в 2 етапи: на першому етапі із загалу хворих на ЦД 2 типу із НАЖХП було відібрано тих, у яких переважали прояви фіброзу печінки (F2 та більше) згідно з результатами еластографії печінки та використання шкал *Вонасіні* та *Metavir*. Кількість таких пацієнтів становила 29, що становило 40,3% від загальної кількості хворих основної групи. Решту пацієнтів було розподілено на 2 підгрупи: в 11 хворих (15,3%) переважали явища неалкогольного стеатозу печінки, у 32 пацієнтів (44,4%) – ознаки неалкогольного стеатогепатиту (НАСГ). У результаті проведеного дослідження встановлено, що наявність фіброзу печінки у хворих на ЦД 2 типу із НАЖХП достовірно частіше пов'язана із серцево-судинними ускладненнями, такими як артеріальна гіпертензія, ішемічна хвороба серця, інфаркт міокарду, інсульт, діабетична ретинопатія та нефропатія. Виявлено достовірне зменшення фракції викиду (ФВ) у хворих на ЦД 2 типу із супутньою НАЖХП. При цьому кількість хворих із порушенням ФВ різного ступеня в основній групі значно перевищувала такий показник у групі порівняння (33,3% і 6,7% відповідно, $p < 0,001$). Середні значення маси міокарда лівого шлуночка достовірно менші у хворих із НАСГ та при формуванні фіброзу порівняно із пацієнтами із НАЖХП на стадії жирового гепатозу. Також виявлено достовірне зменшення розмірів лівого та правого передсердя у хворих із НАСГ порівняно як із пацієнтами зі стеатозом, так і хворими, у яких переважають фіброзні зміни печінки. Для пацієнтів із переважаючими фіброзними змінами в печінці характерно відносно зниження маси міокарда, зменшення кінцевого діастолічного та систолічного об'ємів і ФВ, що може свідчити про розвиток у них діастолічної дисфункції. Показано необхідність урахування в клінічній практиці не лише загальноприйнятих стадій НАЖХП, але й переважаючого патологічного процесу в печінці у хворих на ЦД 2 типу, а саме стеатозу, проявів запалення та фіброзних порушень. Доведено, що фіброзні зміни в печінці можуть розвиватись на всіх етапах ураження печінкової тканини.

Diabetes mellitus (DM) is recognized by WHO experts as noninfectious epidemic and is a serious medical and social problem.

In 2019, 9.3% of the adult population aged 20 to 79 years (463 million) worldwide had diabetes. It is expected that by 2045 the number of patients will increase to 700 million people [14]. The prevalence of DM in Ukraine is 9.1% (men – 8.3%, women – 9.7%). Among the risk factors for diabetes are overweight – 57.3% (men – 58.2%, women – 56.6%), obesity – 21.7% (men – 17.9%, women – 24.9%), sedentary lifestyle – 14.4% (men – 12.2%, women – 16.2%) [15].

In the structure of diabetes, the largest proportion is type 2 diabetes mellitus (T2DM) (90%); the

number of such patients in the world reaches about 417 million people and annually increases by 5-7% [14]. Cardiovascular diseases have been diagnosed in 32.2% of patients with T2DM. They are the cause of death in about 60% of such patients. The risk of developing coronary heart disease (CHD) in patients with T2DM is 2-4 times higher, and the risk of acute myocardial infarction (MI) is 6-10 times higher than in the general population of patients [17].

Another common complication of T2DM is the formation of non-alcoholic fatty liver disease (NAFLD). The disease is characterized not only by the affection of the liver itself with impairment of function, it triggers an entire cascade of pathological changes, among which fibrosis takes an important

place. In our opinion, it is important to consider fibrosis in NAFLD as a systemic lesion of various organs and tissues, not just the liver. From this point of view, fibrosis should be regarded as one of the main components in the progression of most cardiovascular diseases, including CHD.

The development of fibrotic changes in the myocardium leads to a decrease in its elastic properties and diastolic dysfunction, deterioration of myocardial contractility and the formation of systolic dysfunction, impaired heart rhythm and impaired blood flow in coronary arteries.

It is important not only to interpret fibrosis as a typical pathological process, but also to evaluate it as a systemic lesion of various organs and tissues. Of particular interest is the identification of biomarkers of myocardial fibrosis, available for determination in circulation.

Understanding fibrosis as an important factor in the development of various organs dysfunction, ensuring the systemic nature of most diseases, leads to its evaluation as a promising therapeutic target. Further investigation of myocardial fibrosis should be aimed at improving the efficiency of diagnosis and prognosis of its course, as well as carrying out pathogenetically justified therapy.

The aim of the study: to determine the relationship between the degree of liver fibrosis progression and the risk of cardiovascular complications in patients with T2DM with NAFLD.

MATERIALS AND METHODS OF RESEARCH

110 patients with T2DM were examined. Among them there were 62 men and 48 women. The average age was 52.07 ± 1.11 years. All patients were divided into 2 groups: the main group included 72 patients with type 2 DM with concomitant NAFLD, among them – 38 men and 34 women; the control group included 38 patients with T2DM without clinical manifestations of NAFLD (24 men and 14 women).

All patients with T2DM were diagnosed according to WHO criteria (1999, 2006 revision). The diagnosis of NAFLD was established on the basis of anamnesis, clinical, biochemical and ultrasound (US) examinations (EASL-EASD-EASO Clinical Practice Guidelines, 2016).

The patients of the main group were divided into 3 subgroups due to the prevalent pathological processes in the clinical picture. At first we selected patients with T2DM and NAFLD, who had predominant manifestations of liver fibrosis (F2 and more) according to the results of liver elastography and Bonacini and Metavir scales [9, 10]. The number of such patients was 29 accounting for 40.3% of the total number of patients in the main group. The rest of the patients were divided into 2 subgroups: 11

patients (15.3%) had non-alcoholic liver steatosis and other 32 patients (44.4%) had signs of non-alcoholic steatohepatitis (NASH) [16].

All patients were subjected to blood pressure measurements, basic clinical and biochemical studies, electrocardiographic examination (ECG) and echocardiographic examination (echocardiography) performed on Hitachi apparatus [4, 5]. In echocardiography we evaluated following parameters: left ventricle (LV) end-diastolic diameter (EDD), LV end-systolic diameter (ESD), thickness of the LV posterior wall (PW), thickness of the interventricular septum (IS), size of the left atrium (LA), right atrium (RA), aortic diameter, myocardial mass. The end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF) were also calculated. We also collected anamnesis data on cardiovascular complications such as arterial hypertension (AH), CHD, non-fatal MI, non-fatal stroke, nephropathy, retinopathy [8].

The results were processed using Microsoft Windows7 Home PromOA, Dell xPCG3, Product Key V6CTX-V486D-RQFQR-P9472-TG943, X16-96072. The statistical analysis of the study results was performed using Statistical 13.0 (Stat Soft Inc., USA), serial number ZZS999000009306307DEMO-5. The adequacy of the parameters to normal distribution was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Descriptive statistics parameters for continuous variables were presented as the arithmetic mean and standard deviation. Results which did not follow normal distribution were expressed as median and interquartile range. The probabilities of differences were evaluated using Student's t-criterion for independent samples in normal distribution or the Mann-Whitney U-test for independent samples in a distribution different from normal. The relationship between two variables was measured by using Spearman correlation coefficient. A P value <0.05 was considered statistically significant [3].

RESULTS AND DISCUSSION

Prevalence of vascular complications of DM is presented in the Table 1.

Presented data show that the incidence of cardiovascular complications, namely AH, CHD, non-fatal MI, non-fatal stroke, nephropathy, retinopathy was significantly higher in patients with predominance of liver fibrosis. The prevalence of hypertension and retinopathy was also significantly higher in patients with NASH as compared with the control group. The results show the important role of inflammatory and fibrotic changes in patients with T2DM with NAFLD as a risk factor for cardiovascular complications.

Table 1

Prevalence of vascular complications in DM patients with NAFLD and without it

Disease	Control group	T2DM with NAFLD		
		steatosis (NAFL)	NASH	hepatic fibrosis
Arterial hypertension	40%	44.4%	69.4%, $p_c < 0.01$	70.2%, $p_c < 0.001$
CHD	20%	37%	36.45	53.2%, $p_c < 0.001$
Non-fatal MI	0	3.7%	1.75	14.9%, $p_c < 0.001$
Non-fatal stroke	0	0	0	3.2%, $p_c < 0.001$
Nephropathy	10%	25.95	18.25	26.6%, $p_c < 0.001$
Retinopathy	20%	40.75	50.4%, $p_c < 0.01$	67%, $p_c < 0.001$

Note. p_c – reliability compared with control group

Structural reconstruction of the LV myocardium, which occurs in a number of pathological conditions, first of all is manifested in the form of its hypertrophy, so the control of the myocardium condition and the evaluation of possible causes of increase in the thickness of its wall is important in terms of timely treatment and prevention of cardiovascular complications in patients with T2DM and NAFLD (Table 2).

As can be seen from the above data, T2DM is a factor that influences myocardial weight gain. The average myocardial mass of LV significantly exceeds the normative values in patients (up to 224 g in men and up to 162 g in women). Myocardial mass of LV in patients with T2DM with concomitant NAFLD is significantly higher than in patients without NAFLD, especially in women. Thus, we can speak of a greater tendency to development of hypertrophy of the LV in patients with T2DM with concomitant NAFLD.

Thickness of LVPW in patients with T2DM and NAFLD did not differ significantly from this indicator in the control group, only in women with NAFLD the LVPW (1.29 ± 0.02 mm) significantly exceeded the one in the control group (1.20 ± 0.06 mm, $p < 0.05$).

Thickness of LVIS in patients with T2DM and NAFLD (1.36 ± 0.03 mm) was significantly greater than it in the control group (1.26 ± 0.03 mm, $p < 0.05$), especially in women (1.36 ± 0.04 mm and 1.19 ± 0.06 mm, $p < 0.05$).

No significant difference was found between mean aortic diameter in patients of both groups. This

indicator also did not differ significantly between men and women.

It is known that the risk of cardiovascular events is quite closely related to the size of the LA, so its determination in patients with T2DM was aimed at both understanding the extent of LA and assessing the risk of these events. The results obtained showed that the average size of LA in patients with T2DM with concomitant NAFLD significantly exceeded this indicator in the control group (40.00 ± 0.53 mm and 39.00 ± 0.48 mm, respectively, $p < 0.05$), especially in women (39.44 ± 0.42 mm and 38.00 ± 0.82 mm, $p < 0.05$). Other data were obtained regarding the size of the RA. The mean values of this index were higher in the control group (38.26 ± 0.37 mm and 39.59 ± 0.52 mm, respectively, $p < 0.05$), which was more typical for men (37.83 ± 0.56 mm and 40.60 ± 0.67 mm, $p < 0.05$).

The functional state of the heart was evaluated by the indicators of EDV, ESV and EF. It was found that EDV in patients with T2DM and NAFLD significantly exceeded it in the control group (125.48 ± 5.30 ml and 109.56 ± 5.88 ml, $p < 0.05$), both in men (131.85 ± 8.02 ml and 118.82 ± 7.76 ml, $p < 0.05$) and in women (117.20 ± 6.56 ml and 95.00 ± 8.06 ml, $p < 0.01$). ESV was also higher in patients of the main group (52.43 ± 3.08 ml and 41.56 ± 4.45 ml, respectively, $p < 0.05$), with this difference being most pronounced in women (48.60 ± 3.45 ml and 29.14 ± 2.87 ml, respectively, $p < 0.01$).

Table 2

EchoEG results of patients with T2DM and NAFLD (M±m)

Index	Gender	T2DM with NAFLD, n= 72	T2DM without NAFLD, n= 38	p
Myocardial mass of LV, g	Total	319.79±13.53	271.61±11.94	<0.01
	Males	321.83±21.49	287.00±16.54	
	Females	317.34±14.91	247.43±15.30	<0.01
LVPW, mm	Total	1.31±0.02	1.26±0.03	
	Males	1.33±0.03	1.30±0.03	
	Females	1.29±0.02	1.20±0.06	<0.05
Thickness of IS, mm	Total	1.36±0.03	1.26±0.03	<0.05
	Males	1.35±0.04	1.30±0.03	
	Females	1.36±0.04	1.19±0.06	<0.05
Aortic diameter, mm	Total	33.73±0.35	33.73±0.43	
	Males	34.33±0.32	33.89±0.55	
	Females	33.00±0.69	33.50±0.73	
LA, mm	Total	40.00±0.53	39.00±0.48	<0.05
	Males	40.38±0.84	39.64±0.57	
	Females	39.44±0.42	38.00±0.82	<0.05
RA, mm	Total	38.26±0.37	39.59±0.52	<0.05
	Males	37.83±0.56	40.60±0.67	<0.05
	Females	39.00±0.38	38.14±0.71	
EDV, ml	Total	125.48±5.30	109.56±5.88	<0.05
	Males	131.85±8.02	118.82±7.76	<0.05
	Females	117.20±6.56	95.00±8.06	<0.01
ESV, ml	Total	52.43±3.08	41.56±4.45	<0.05
	Males	55.38±4.68	49.45±6.57	
	Females	48.60±3.45	29.14±2.87	<0.01
EF, %	Total	57.76±1.27	63.07±0.96	<0.01
	Males	57.91±1.42	63.33±1.31	<0.05
	Females	57.60±2.01	62.67±1.54	<0.05
Proportion of patients with reduced EF, %	Total	33.3	6.7	<0.001

There was also a significant decrease in EF in patients with T2DM with concomitant NAFLD (57.76±1.27% and 63.07±0.96%, $p<0.01$), both in men (57.91±1.42% and 63.33±1.31%, $p<0.05$) and

women (57.60±2.01% and 62.67±1.54, respectively, $p<0.05$). At the same time, the number of patients with decreased EF in the main group significantly

exceeded this indicator in the control group (33.3% and 6.7%, respectively, $p < 0.001$)

To assess the role of liver fibrotic changes in the formation of cardiac dysfunction, the analysis of heart structure and function in patients with T2DM and different stages of NAFLD was done (Table 3).

As can be seen from the presented data, the mean values of LV myocardial mass are significantly lower in patients with NASH and in the formation of fibrosis as compared with patients with NAFLD at the stage of fatty hepatosis. There was also a significant reduction in the size of the LA and RA in patients with NASH compared with patients with steatosis and patients with predominant liver fibrosis.

The progressive reduction of EDV in patients with NAFLD at the stage of NASH compared with the stage of steatosis continues in the stage of liver fibrosis. The natural result of such morphological changes in the myocardium is the deterioration of the functional properties of the heart, namely the reduction of the EF in patients with NAFLD at the stage of NASH and at the stage of fibrotic changes. The same data are confirmed by the analysis of the number of patients with reduced EF in the groups of T2DM with NAFLD and in the control group. It was found that the percentage of patients suffering from type 2 diabetes with concomitant NAFLD was significantly higher ($33.3 \pm 8.7\%$) compared with the group of patients with T2DM without NAFLD ($6.7 \pm 4.06\%$, $p < 0.01$).

Table 3

Indicators of heart structure and function in patients with T2DM with different stages of NAFLD (M±m)

Index	Steatosis (s), n=11	NASH (sh), n=32	Fibrosis (f), n=29	p
Myocardial mass of LV, g	404.00±17.10	274.83±12.04	250.00±13.05	$p_{s-sh} < 0.001$ $p_{s-f} < 0.001$
LVPW, mm	1.40±0.05	1.29±0.05	1.30±0.05	
Thickness of IS, mm	1.45±0.05	1.26±0.03	1.30±0.05	$p_{s-sh} < 0.01$ $p_{s-f} < 0.05$
Aortic diameter, mm	36.0±0.57	32.80±1.04	32.50±0.25	$p_{s-sh} < 0.01$ $p_{s-f} < 0.01$
LA, mm	40.0±0.51	38.0±0.74	42.50±0.75	$p_{s-sh} < 0.05$ $p_{sh-f} < 0.001$
RA, mm	40.0±0.53	37.40±0.79	39.0±0.65	$p_{s-sh} < 0.01$
EDV, ml	189.00±5.60	124.67±7.75	106.00±3.00	$p_{s-sh} < 0.001$ $p_{s-f} < 0.001$ $p_{sh-f} < 0.05$
ESV, ml	58.00±5.02	54.67±3.13	48.50±4.25	
EF, %	66.0±2.50	57.40±3.31	54.00±2.50	$p_{s-sh} < 0.05$ $p_{s-f} < 0.01$
% patients with decreased EF		40%		

T2DM, NAFLD and cardiovascular disease have common pathogenetic mechanisms, so all patients with T2DM should be screened for both liver pathology and cardiovascular disease risk assessment. The liver plays a significant role in the development of abdominal obesity and insulin resistance, atherogenic dyslipidemia. Obesity leads to inflammation of adipose tissue, characterized by cellular infiltration, fibrosis, changes in microcir-

ulation, impaired adipokine secretion and metabolism in adipose tissue, as well as accumulation in the blood of nonspecific markers of inflammation [1, 13].

Obesity is considered as an independent risk factor for the development of cardiovascular disease and one of the main links, and possibly the trigger mechanism of other risk factors, in particular AH, and their coexistence has a greater impact on the

structure and function of the LV than each of them separately [6, 7, 11, 12, 18].

On the other hand, liver fibrosis is an important risk factor for the formation of cardiovascular disorders, which is a manifestation of a generalized process in the body and affects all systems including the cardiovascular system. Our results indicate the need to consider not only the common stages of NAFLD, but also the predominant pathological process in the liver in patients with T2DM, namely steatosis, inflammation manifestations (NASH) and fibrotic disorders. It should be noted that it is fibrotic changes in the liver that can develop at all stages of liver tissue damage.

The development of liver fibrosis in patients with T2DM with NAFLD is significantly more often associated with cardiovascular complications such as AH, coronary heart disease, MI, stroke, diabetic retinopathy and nephropathy.

The differences in left ventricular myocardial mass revealed in patients with various manifestations of NAFLD, namely with the predominance of steatohepatitis, NASH, fibrosis, require further study and consideration of left ventricular mass index. Such approach was described in [2], which showed that the severity of fibrotic changes in the liver and myocardium depends on the progression of NAFLD and the stage of fibrosis, and the presence of CHD and NAFLD explain unidirectional fibrosis processes in both the liver and myocardium.

As can be seen from the presented data, the mean values of LV myocardial mass are significantly lower in patients with NASH and formation of fibrosis as compared with patients with NAFLD at the stage of fatty hepatosis. There was also a significant reduction in the size of the LA and RA in patients with NASH compared with patients with steatosis and patients with predominant liver fibrosis. An increase in myocardial mass at the stage of steatosis may indicate the development of hypertrophic processes in the myocardium. Patients with predominant fibrotic changes in the liver are cha-

racterized by a relative decrease in myocardial mass, decrease in EDV, ESV, and EF, which may indicate the development of diastolic dysfunction in them.

CONCLUSIONS

1. The presence of liver fibrosis in patients with T2DM with NAFLD is significantly more commonly associated with cardiovascular complications such as AH, CHD, MI, stroke, diabetic retinopathy and nephropathy.

2. It was revealed the tendency to increase the mass of myocardium in patients with T2DM and NAFLD due to the formation of left ventricular and left atrial hypertrophy.

3. Significant reduction of EF in patients with T2DM with concomitant NAFLD was found. At the same time, the number of patients with disorders of EF of varying degrees in the main group significantly exceeded this indicator in the control group (33.3% and 6.7%, respectively, $p < 0.001$).

4. The mean myocardial mass of LV was significantly lower in patients with NASH and fibrosis compared with patients with NAFLD at the stage of fatty hepatosis. There was also a significant reduction in the size of the LA and RA in patients with NASH as compared with patients with steatosis and patients with predominant liver fibrosis. Patients with predominant fibrotic changes in the liver were characterized by a relative decrease in myocardial mass, a decrease in EDV, ESV, and EF, which may indicate the development of diastolic dysfunction in them.

5. The need to consider in clinical practice not only the common stages of NAFLD, but also the predominant pathological process in the liver in patients with T2DM, namely steatosis, manifestations of inflammation (NASH) and fibrotic disorders is shown. It has been proved that fibrotic changes in the liver can develop at all stages of liver tissue damage.

Conflict of interest. The authors declare no conflict of interest.

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